From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/EP2004/013538	International filing date *(day/month/year)* 29.11.2004
Priority date *(day/month/year)* 07.05.2004	
International Patent Classification (IPC) or both national classification and IPC C12N9/14, C12N15/11, A61K31/713, C12Q1/34	
Applicant CELLZOME AG	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-6,13 and 15-17 (all in part) and claims 11,12 and 14

because:

☒ the said international application, or the said claims Nos. 16 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-6,13 and 15-17 (all in part) are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☒ the claims, or said claims Nos. 1-6,13 and 15-17 (all in part) are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 11,12 and 14

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-5,7-10,17
	No:	Claims	1,6,13,15 and 16
Inventive step (IS)	Yes:	Claims	2-5,7-10,17
	No:	Claims	1,6,13,15 and 16
Industrial applicability (IA)	Yes:	Claims	1-10,13,15 and 17
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Prior art

Reference is made to the following document:

D1: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 100, no. 24, (25 November 2003), pages 14187-14192 [XP002339932]

Item I. Basis of the report

The required statements that the subsequently filed sequence listing does not comprise new subject-matter to that in the application as filed have not been furnished to the ISA.

Item III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1. Claims 1-6 and 11-17 relate to (a) compound(s) defined by reference to a desirable characteristic or property, namely their capacity to interact with ATP7A and/or with gamma-secretase and/or beta-secretase. The claims cover all compounds having this characteristic or property, whereas the application provides support and/or disclosure within the meaning of Articles 5 and 6 PCT for only a very limited number of such compounds. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Therefore, present opinion is restricted to the subject-matter clearly disclosed, i.e. to the siRNAs as defined in example 2 (see also Item V.).
As no search could be done for present claims 11,12 and 14, said claims will not be considered in this opinion.

III.2. Claim 16 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Item V. Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1. NOVELTY (Art. 33(2) PCT) and INVENTIVE STEP (Art. 33(3) PCT)

V.1.1. None of the available prior art documents discloses or suggests the use of siRNAs targeting ATP7A, especially of SEQ IDs 3 and 4 as disclosed in example 2, in the treatment of neurodegenerative diseases such as Alzheimer's disease. The same is valid for the relationship between ATP7A inhibition and the modulation of the activity of γ- and/or β-secretases. Hence, present claims 1-10,13 and 15-17 (as far as siRNAs are concerned) fulfill the requirements of novelty and inventive step as set out in Art. 33(2) and 33(3) PCT.

V.1.2. However, concerning the general concept of ATP7A modulation, it has to be noted that D1 discloses that the dietary supplementation of copper (an ATP7A interactor) shows a beneficial effect on APP-transgenic mice by decreasing Aβ neo-formation. As such, it is detrimental to the novelty of claims 1,6,13,15 and 16.

V.2. INDUSTRIAL APPLICABILITY (Art. 33(4) PCT)

V.2.1. For the assessment of the present claim 16 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V.2.2. The subject-matter of claims 1-10,13,15 and 17 is considered as being industrially applicable in the sense of Art. 33(4) PCT.

Item VIII. Certain observations on the international application

The overall correlation between ATP7A modulation (especially inhibition) and its beneficial effects on neurodegenerative diseases is not clear (Art. 6 PCT). Indeed, from the available prior art it seems that the consequences of ATP7A inhibition will be opposite when considering Alzheimer disease or Menkes disease. Therefore, the generalisation of the use of siRNAs in the treatment of any neurodegenerative disease is questionned. Similarly, an automatic effect of siRNA suppression of ATP7A expression on the activity of γ- and/or β-secretases is not disclosed neither in the application which does therefore not meet the requirements of Art. 5 and 6 PCT.